



10/030, 868

GJE

I, Doran R. Pace, certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
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REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. GJE-81
Patent No. 6,929,934

Doran R. Pace, Patent Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Yuri Evgenievich Korchev, David Klenerman, Max Joseph Lab
Issued : August 16, 2005
Patent No. : 6,929,934
For : Optical Microscopy and its Use in the Study of Cells

Certificate

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SEP 08 2005

of Correction

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where the error occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:

Column 10, line 48:

“while dose to”

Application Reads:

Amendment Under 37 CFR §1.116 dated February 16, 2005 (original claim 53, re-numbered claim 32):

--while close to--

A true and correct copy of the February 16, 2005 Amendment Under 37 CFR §1.116 which supports Applicants' assertion of error on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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DRP/kmm

Attachments: Certificate of Correction,
Copy of Amendment Under 37 CFR §1.116

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,929,934

Page 1 of 1

APPLICATION NO.: 10/030,868

DATED : August 16, 2005

INVENTORS : Yuri Evgenievich Korchev, David Klenerman, Max Joseph Lab

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,

Line 48, "while dose to" should read --while close to--.

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COPY**CONFIDENTIAL**

I hereby certify that this correspondence is being
facsimile transmitted to the United States Patent
and Trademark Office on February 16, 2005.



Doran R. Pace, Patent Attorney



AMENDMENT UNDER 37 CFR §1.116
Examining Group 1651
Patent Application
Docket No. GJE-81
Serial No. 10/030,868

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Susan Marie Hanley
Art Unit : 1651
Applicants : Yuri Evgenievich Korchev, David Klenerman, Max Joseph Lab
Serial No. : 10/030,868
Filed : October 18, 2001
Conf. No. : 8909
For : Optical Microscopy and its Use in the Study of Cells

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Commissioner for Patents
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AMENDMENT UNDER 37 CFR §1.116

Sir:

In response to the Office Action dated November 16, 2004, please amend the above-identified patent application as follows:

In the Claims

1-17 (canceled)

18 (currently amended). An apparatus for imaging an object, comprising a probe via which an assay component may be delivered; means for vibrating the probe, at a given frequency, substantially normal to the surface of the object; a sensor to detect ion current; means for monitoring modulation of the ion current resulting from the vibration of the probe at the given frequency while close to the surface of the object; and means to control the distance of the probe from the surface of the object in response to the modulation of the ion current.

19 (previously presented). The apparatus according to claim 18, wherein the probe is a micropipette.

20 (previously presented). The apparatus according to claim 18, wherein the assay component is light.

21 (previously presented). The apparatus according to claim 19, wherein the assay component is light.

22 (previously presented). The apparatus according to claim 20, wherein the probe comprises a fiber optic.

23 (previously presented). The apparatus according to claim 20, which additionally comprises a laser light source.

24 (previously presented). The apparatus according to claim 22, which additionally comprises a laser light source.

25 (previously presented). The apparatus according to claim 20, wherein the probe contains a light-activatable dye at its tip.

26 (previously presented). The apparatus according to claim 20, wherein the outer surface of the probe is coated to prevent leakage of light.

27 (previously presented). The apparatus according to claim 20, wherein the outer surface of the probe is coated with a metal layer to prevent leakage of light.

28 (previously presented). The apparatus according to claim 18, wherein the probe contains, as the assay component, a substance that, at the surface of a live cell, produces a detectable change.

29 (previously presented). The apparatus according to claim 19, wherein the probe contains, as the assay component, a substance that, at the surface of a live cell, produces a detectable change.

30 (previously presented). The apparatus according to claim 28, wherein said substance generates fluorescence, bioluminescence or chemiluminescence.

31 (previously presented). The apparatus according to claim 29, wherein said substance generates fluorescence, bioluminescence or chemiluminescence.

32 (previously presented). The apparatus according to claim 18, wherein the probe contains, as the assay component, a substance that, on delivery to a live cell, produces a detectable change inside the cell.

33 (previously presented). The apparatus according to claim 19, wherein the probe contains, as the assay component, a substance that, on delivery to a live cell, produces a detectable change inside the cell.

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34 (canceled).

35 (currently amended). A method for imaging an object in a liquid environment, by scanning ion conductance microscopy, which comprises vibrating a probe, at a given frequency, substantially normal to the surface of the object, detecting ion current, monitoring modulation of the ion current resulting from the vibration of the probe while close to the surface of the object, controlling the distance of the probe from the surface of the object in response to the modulation of the ion current, wherein the probe includes means for delivering an assay component to the object.

36 (previously presented). The method according to claim 35, wherein the probe is a micropipette.

37 (previously presented). The method according to claim 35, wherein the probe comprises a fiber optic.

38 (previously presented). The method according to claim 35, wherein the probe contains a light-activatable dye at its tip.

39 (previously presented). The method according to claim 35, wherein the outer surface of the probe is coated with a metal layer to prevent leakage of light.

40 (previously presented). The method according to claim 35, wherein the probe contains, as the assay component, a substance that, at the surface of a live cell, produces a detectable change.

41 (previously presented). The method according to claim 36, wherein the probe contains, as the assay component, a substance that, at the surface of a live cell, produces a detectable change.

42 (previously presented). The method according to claim 41, wherein said substance generates fluorescence, bioluminescence or chemiluminescence.

43 (previously presented). The method according to claim 35, wherein the probe contains, as the assay component, a substance that, on delivery to a live cell, produces a detectable change inside the cell.

44 (previously presented). The method according to claim 36, wherein the probe contains, as the assay component, a substance that, on delivery to a live cell, produces a detectable change inside the cell.

45 (previously presented). The method according to claim 35, wherein the assay component is light.

46 (previously presented). The method according to claim 45, which additionally comprises a laser light source.

47 (previously presented). The method according to claim 35, wherein the probe contains, as the assay component, a substance that, at the surface of a live cell, produces a detectable change.

48 (previously presented). The method according to claim 47, wherein said substance generates fluorescence, bioluminescence or chemiluminescence.

49 (previously presented). The method according to claim 35, wherein the probe contains, as the assay component, a substance that, on delivery to a live cell, produces a detectable change inside the cell.

50 (previously presented). The method according to claim 35, which comprises generating light and wherein the said distance is less than the wavelength of the light.

51 (canceled).

52 (previously presented). The method according to claim 35, wherein the object is a live cell.

53 (new). An apparatus for imaging an object, comprising a probe, wherein the probe includes or contains an assay component that can be delivered to a locus of observation, wherein the assay component is a chemical or physical entity; means for vibrating the probe, at a given frequency, substantially normal to the surface of the object; a sensor to detect ion current; means for monitoring modulation of the ion current resulting from the vibration of the probe at the given frequency while close to the surface of the object; and means to control the distance of the probe from the surface of the object in response to the modulation of the ion current.

54 (new). The apparatus according to claim 53, wherein the probe is a micropipette.

Remarks

Claims 18-33, 35-50, and 52 are pending in the subject application. By this Amendment, Applicants have amended claims 18 and 35 and added new claims 53 and 54. Support for the amendments and new claims can be found throughout the subject specification, including, for example, at page 3, lines 32-33, and in the claims as originally filed. Entry and consideration of the amendments and new claims presented herein is respectfully requested. Accordingly, claims 18-33, 35-50, 53, and 54 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As the Examiner has not reiterated the informalities objection from the Office Action dated April 23, 2004, Applicants assume the Examiner has withdrawn the objections to the claims.

Claims 18-27, 35-39, 50, and 52 remain rejected under 35 USC §102(b) as anticipated by Lewis *et al.* (U.S. Patent No. 4,917,462). The Examiner asserts that the Lewis *et al.* patent discloses a near field scanning optical microscopy (NSOM) apparatus involving a metal-coated glass pipette having a thin tip and means for determining the proximity of the aperture of the pipette to a surface. The Examiner also asserts that the Lewis *et al.* patent teaches the application of an electrical potential between the pipette and the stage, resulting in a measurable current to provide a feedback signal used to determine and control the distance between aperture and object as one of the possible means. Applicants respectfully traverse this grounds of rejection.

Applicants respectfully submit that the claimed invention is not anticipated or obvious over the cited references. It appears from the Examiner's comments in the Office Action that there may be some misunderstanding of Applicants' claimed invention. Thus, clarification of terminology used in the claims may be helpful to the Examiner in understanding Applicants' claimed invention and the distinction over the Lewis *et al.* device. In this regard, Applicants respectfully assert that the term "vibrate" or "vibrating" as used in the subject claims does not merely mean to move back and forth but to do so rapidly. Webster's dictionary uses the term "periodic." Further, the term "vibrate" is used in the context of the subject application to mean to move back and forth at a given or defined frequency.

A critical distinction between Applicants' claimed invention and the device of the Lewis *et al.* patent is that the Lewis *et al.* device does not impose vibration on the probe. It can be understood

from the portion of the Lewis *et al.* patent referenced by the Examiner (*i.e.*, column 11, lines 27-52) that a small potential is applied between the pipette and the electrically conductive stage in order to generate a measurable current. The generated current varies with the distance between the surface of the object and the tip of the pipette (see column 11, lines 36-38, of the Lewis *et al.* patent). The device of the Lewis *et al.* patent then detects the current and moves the pipette up or down as it scans along the object so as to keep the detected current constant and thereby keep the pipette a constant distance from the surface of the object and produces a topographical map of the surface of the object being studied. Applicants respectfully assert that what the Examiner may consider to be "vibration" of the pipette in the Lewis *et al.* patent is not periodic at a defined frequency.

By contrast, in the present invention, rather than striving for a constant distance and current as is the case for the device of the Lewis *et al.* patent, the probe of Applicants' device is itself actively vibrated, producing a periodically varying distance and generating a corresponding periodically varying signal (modulated current (I_{mod})) to control the probe-sample mean distance and/or minimum distance during each cycle of the vibration. In particular, the subject invention involves actively vibrating the probe vertically at a defined frequency and using the signal at this same frequency to adjust the vertical position of the pipette relative to the surface of the object. As noted above, the Lewis *et al.* patent simply moves the pipette vertically (it is not vibrated), back and forth in order to keep the ion current constant. The movement of the pipette in the Lewis *et al.* patent is not at any defined frequency; it is just in response to changes in topography in order to maintain a constant current.

The active vibration utilized with the present invention is important since the signal generated is very different from anything disclosed in or observed with the Lewis *et al.* patent. In Applicants' claimed invention, the probe is used to produce a signal that allows for interpretation and control. There is only a signal when the probe is close to the surface and the signal increases as the probe approaches the surface. This results in a bigger and bigger signal, which can be interpreted by the device to move the probe away from the surface. If one does not actively vibrate the probe at a defined frequency, the current is present at any distance from the surface and gets smaller as the probe gets closer. This makes approach to the surface and distance control much more difficult. Thus, active vibration, at a defined frequency, is imposed on the probe of the claimed invention,

regardless of the probe-object distance and the modulated signal is the control signal at this frequency. In summary, the present invention utilizes periodic, rapid movement of the probe, to generate an AC current and a controllable signal. The Lewis *et al.* patent does not teach or suggest actively vibrating the pipette of their device at a defined frequency.

For purposes of clarification only, claims 18 and 35 have been amended to indicate that the probe is vibrated at a given frequency. Support for the amendment can be found throughout the subject specification, including, for example, at page 6, line 23. It is well settled in patent law that the claim language of an amendment need not be disclosed word for word in a specification. *In re Wilder*, 222 USPQ 369, 372 (Fed. Cir. 1984) (“It is not necessary that the claimed subject matter be described identically, but the disclosure must convey to those skilled in the art that applicant had invented the subject matter later claimed.”) (emphasis added). Applicants believe that the amendments to claims 18 and 35 presented herein make it clear that the present invention is novel and distinct from the device of the Lewis *et al.* patent. In particular, it should now be clear that the vibration of the probe of Applicants’ claimed invention is something other than simple movement along the z axis (vertical), as described by the Lewis *et al.* patent, and that the vibration is superimposed on that simple vertical movement. The vibration is imposed at a given or defined frequency, and knowledge of that frequency allows control. Where the subject specification refers to “frequency-modulated,” it is that frequency that is to be understood.

As the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). Applicants respectfully assert that the Lewis *et al.* patent does not teach each and every element of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claims 18-33, 35-50, and 52 remain rejected under 35 USC §103(a) as obvious over Lewis *et al.* (U.S. Patent No. 4,917,462) in view of Islam (U.S. Patent No. 5,485,536) and further in view of Tan (1988). The Lewis *et al.* patent is relied upon by the Examiner as set forth in the rejection under 35 USC §102(b). The Examiner asserts that it would be obvious for an ordinarily skilled artisan to use a fiber optic probe as taught by the Islam patent in an NSOM device. The Tan reference is cited

as teaching that it is routine in the art to probe cells with substances that produce visible and fluorescent light and to use a pipette probe to deliver the substances. Applicants respectfully traverse this grounds of rejection.

Applicants respectfully assert that the references cited by the Examiner, taken alone or in combination, do not teach or suggest the claimed invention. Applicants hereby incorporate their remarks regarding the Lewis *et al.* patent, as set forth herein in regard to the rejection under 35 USC §102(b). As noted previously, the Lewis *et al.* patent does not teach or suggest actively vibrating a pipette of the device at a defined frequency. The secondary references relied upon by the Examiner do not cure the deficiencies of the Lewis *et al.* patent. Applicants respectfully assert that neither the Islam patent nor the Tan reference describes the feature of active vibration of a probe at a defined frequency.

By this Amendment, Applicants have presented new independent claim 53, similar to claim 18, but in which the presence of “a chemical or physical entity” is specified as a reagent in the probe. This is distinct from the use of light as the “reagent,” as described in the Tan reference. The claim is directed to the local application of reagents from the probe for local assays of the cell surface just under the probe rather than by adding the reagent from a nearby micropipette. This is done using a fine probe, close to the surface, at a controlled distance. Since topography can also be measured, the present invention allows the user to know the exact location of the probe relative to, for example, a cell surface and where the response or measurement is made.

As the Examiner is aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicants respectfully assert that the cited references do not teach or suggest Applicants’ claimed invention, nor do the references provide the requisite reasonable expectation of success. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

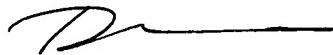
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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